ENVIRONMENTALLY BENING CATALYSIS: CHITOSAN, A NATURAL LIGAND FOR HIGHLY ENANTIOSELECTIVE RU CATALYZED TRANSFER HYDROGENATION OF KETONES

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Abstract

We have studied the use of an in situ prepared Ru-chitosan complex in the transfer hydrogenation of prochiral ketones. Reaction of acetophenone and its substituted derivatives resulted in good enantioselectivities in aqueous solvent mixture. To our delight in the reduction of several cyclic ketones over 90% enantiomeric excesses were obtained, reaching up to 97% in the transfer hydrogenation of heterocyclic 4-chromanone or 4-thiochromanone derivatives. The pre-prepared Ru-chitosan complex provided identical results even after several months' storage without special precautions. The complex prepared from a natural, inexpensive, readily available chiral ligand is a convenient alternative of the synthetic ligands, and may be applied in environmentally friendly and sustainable processes for preparing optically pure chiral alcohols.

Scope

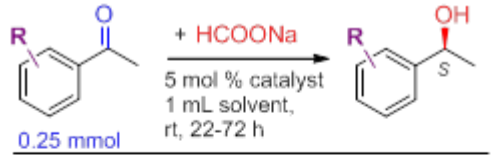
Enantioselective hydrogenations and transfer hydrogenations are among the most convenient procedures in the preparation of optically pure compounds used as intermediates in the production of pharmaceuticals, agrochemicals, flavors and fragrances.[1] A large variety of chiral complexes have been developed for the transfer hydrogenation of various prochiral unsaturated compounds. Recent trends in the fine chemical industry require environmentally friendly, sustainable processes. The use of chiral ligands of natural origin, such as chitosan, has multiple advantages. Chitosan may be obtained from wastes produced in the food industry, may replace the expensive chiral ligands, is biocompatible, biodegradable and due to its hydrophilic character may be used in aqueous media. Thus, is a perfect candidate for the development of catalysts used in green processes. Due to the presence of the free amino groups in this biopolymer it may be used as organocatalyst and is able to form complexes with metal cations.[2,3] However, only few studies have been published attempting the use of chitosan complexes in asymmetric transfer hydrogenations and the results obtained until now are far behind the values produced using synthetic chiral ligands. Satisfactory results were obtained using few chitosan derivatives,[4,5] however the need of functionalization of the chiral polymer decreased significantly their practical values.

Our aim was to study the transfer hydrogenation of prochiral ketones using chiral Ru catalysts prepared from unmodified chitosan as ligand in water-based solvents and to explore the applicability of this chiral complex. Determination of the structural requirements imposed to the ligand and the scope of the reaction were set as primary tasks, with the final goal of developing a highly enantioselective, economic, environmentally friendly procedure for the convenient transfer hydrogenation of prochiral ketones.

Results and discussion

Preliminary studies were carried out with an *in situ* prepared complex from [Ru(p-cymene)Cl_2]$_2$ and commercial high molecular weight chitosan using HCOONa as donor in the transfer hydrogenation of a few acetophenone derivatives. Short optimization of the reaction conditions and the solvent composition led us to the conclusion that a water-iPrOH 4-1 solvent mixture provides the best enantioselectivities in these reactions. Investigations of the ligand structure using low molecular weight chitosan, N-, O- and N-,O- functionalized chitosan, glucosamine and chitin indicated that the long polymeric chain and the free amino group is benefic for obtaining good activities and enantioselectivities. Next, we examined the transfer hydrogenation of a large library of aromatic ketones under conditions found most appropriate, selected examples are shown in Figure 1.

Figure 1. Enantioselective transfer hydrogenation of acetophenone derivatives with Ru-chitosan complex.



R	Conv(%)	ee(%)	R	Conv(%)	ee(%)
H	99	78			
3'-Me	94	81	4'-F	92	71
4'-Me	74	82	4'-Cl	93	79
4'-NO_2	99	62	4'-Br	99	82
3'-OMe	99	76	3'-Br	99	80
4'-OMe	70	68	2'-Br	98	51
3'-CF_3	99	85	4'-I	95	82
4'-CF_3	99	82	3',5'-diCF_3	88	86

To our delight, results obtained in our experiments exceeded the best values reported until now by the use of chitosan derivatives as ligand. Further variation in the prochiral ketone structure showed that increasing the alkyl chain of acetophenone decreased the ee (not shown), however, the reduction of ketones having alicyclic structure connected to the aromatic ring gave surprisingly high enantioselectivities, as shown in Figure 2. Moreover, the ketones including a heteroatom in the ring, such as 4-chromanones and 4-thiochromanones provided the corresponding alcohols in even better, up to 97%, enantiomer excesses (Figure 2). The reactions were also carried out at 1 mmol scale to obtain the isolated products in excellent yields and high optical purities.

Further, we prepared the Ru-chitosan complex, which after slow evaporation of the solvent gave a dark orange film (Figure 2.), which was equally efficient in the transfer hydrogenations as the *in situ* formed catalyst. The material could be handled easier, as compared to the parent chitosan and could be stored for several months without alterations in its catalytic properties. The FT-IR spectrum of this material indicated the coordination of the Ru to chitosan.

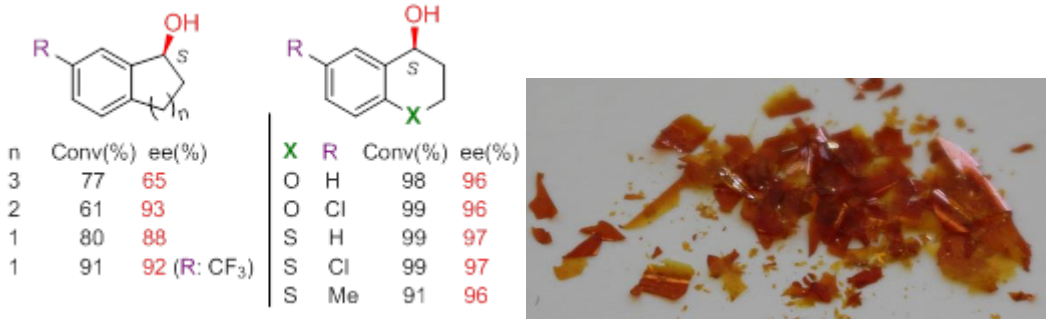


Figure 2. Results of transfer hydrogenation of cyclic ketones with the Ru-chitosan complex and the image of the prepared complex film.

Based on the results obtained using different ligands and the effect of the ketone structure on the conversion and enantioselectivity we suggested a plausible structure for the complex. It is assumed that the amino groups of different glucosamine units are involved in the coordination of the Ru(II) ion. An outer-sphere mechanism is suggested, during which the ketones' six-membered ring assure the necessary rigidity to the molecule, whereas hydrogen-bond acceptor heteroatoms in the ring are able to interact with the hydroxyl groups of the chitosan improving the orientation of the ketone.

Conclusions

In summary, we have examined the performance of commercial chitosan as chiral ligand in the enantioselective transfer hydrogenation of prochiral ketones. Following the optimization of the reaction conditions, especially the nature of the solvent, we obtained high enantioselectivities in the reaction of a large number of acetophenone derivatives in aqueous media. The values surpassed those reported in the literature obtained with chitosan derivatives. Moreover, we obtained over 90% ee in the reaction of cyclic ketones, reaching up to 97% in the reduction of compounds having heteroatoms in the alicyclic ring. The prepared Ru-chitosan complex could be stored several month without special precautions. Based on the effect of chitosan derivatives and other ligands we suggested a plausible structure of the complex and a probable reaction mechanism, which rationalized the effect of the prochiral ketones' structure on the enantioselectivity. Finally, we mention that the highly selective chiral Ru complex was prepared using a cheap, natural material as chirality source, thus the developed method is a green, environmentally friendly and sustainable way to obtain optically enriched chiral alcohols.

Acknowledgments

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